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METHOD OF IMPROVING POST-ISCHEMIC MYOCARDIAL DYSFUNCTION USING AN ACE INHIBITOR ALONE OR IN COMBINATION WITH A THROMBOLYTIC AGENT AND COMBINATION

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(56) Prior Art Documents

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(57) Claim

1. A method of treating post-ischemic myocardial dysfunction in a mammalian species, which comprises initiating within six hours following myocardial infarction administration of an effective amount of captopril alone or in combination with a thrombolytic agent to reduce or eliminate reperfusion injury.

5. The method as defined in any one of claims 1 to 4, wherein the thrombolytic agent is **tissue plasminogen activator (tPA)**, **recombinant tissue plasminogen activator**, streptokinase, urokinase or prourokinase.

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Complete Specification for the invention entitled:

METHOD OF IMPROVING POST-ISCHEMIC MYOCARDIAL DYSFUNCTION USING AN ACE
INHIBITOR ALONE OR IN COMBINATION WITH A THROMBOLYTIC AGENT AND COMBINATION

Our Ref : 149516
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The following statement is a full description of this invention, including
the best method of performing it known to applicant(s):

METHOD OF IMPROVING POST-ISCHEMIC
MYOCARDIAL DYSFUNCTION USING AN
ACE INHIBITOR ALONE OR IN COMBINATION WITH
A THROMBOLYTIC AGENT AND COMBINATION

5

The present invention relates to a method for improving post-ischemic myocardial dysfunction in mammalian species by administering an 10 angiotensin converting enzyme (ACE) inhibitor alone or with a thrombolytic agent such as tPA which may act as scavengers of free oxygen radicals to enhance the recovery of heart function by reducing oxygen demand on the heart, and to such combination 15 of ACE inhibitor and thrombolytic agent.

Blood flow reductions in the heart can result in dysfunction of this organ and cell death 20 if the flow reduction is severe enough. Restoration of coronary blood flow early during a heart attack is becoming a clinical reality with the advent and improvements in thrombolytic, mechanical, and surgical interventions. While 25 early restoration of blood flow, for example, by thrombolysis or following transient ischemia, can prevent or mitigate the degree of cell death (infarction) occurring, reperfusion can still

result in some degree of cardiac dysfunction or cell death (also referred to as stunned myocardia). Thus, it would be of great clinical value to find a means to preserve reperfusion function of the heart.

5 In accordance with the present invention, a method is provided for treating post-ischemic 10 myocardial dysfunction in mammalian species to improve heart function, wherein a therapeutically effective amount of an angiotensin converting enzyme inhibitor (ACE inhibitor) alone or in combination with a thrombolytic agent is systemically 15 administered, such as orally or parenterally, or by catheter, prior to, during or soon after reperfusion, that is, within 4 to 6 hours of a myocardial infarction to mitigate the post-ischemic 20 adverse effects of free radicals on heart function during periods of myocardial occlusion and reperfusion.

The term "reperfusion" is employed herein to refer to release of occlusion and resumption of blood flow.

25 In addition, in accordance with the present invention, there is provided a combination of ACE inhibitor and thrombolytic agent.

The ACE inhibitor and thrombolytic will be employed in a weight ratio to each other of within 30 the range of from about 0.1:1 to about 10:1 and preferably from about 0.4:1 to about 2.5:1.

It has been found that the ACE inhibitor alone or in combination with a thrombolytic agent improves post-ischemic performance of 35 the heart by improving post-ischemic contractile

function when administered during both the coronary occlusion period and the reperfusion period (first 4 to 6 hours after myocardial infarction) or only during the reperfusion period.

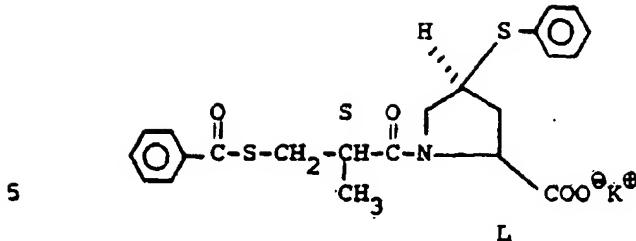
5 Such improvement in post-ischemic performance of the heart is evidenced by decreased contractile dysfunction, decrease in tissue necrosis, reduced myocardial workload, reduced myocardial demand for oxygen and reduced myocardial 10 peripheral work.

The above combination may also be administered in the weeks and months following myocardial infarction to inhibit left ventricle chamber enlargement and wall thinning.

15 The above benefits are achieved primarily through use of a mercapto (-S-) containing ACE inhibitor alone or in conjunction with a thrombolytic agent. Administered simultaneously with the thrombolytic agent, the free radical scavenging effects of the ACE inhibitor would prevent reperfusion injury which develops when 20 blood flow is restored to a previously ischemic area.

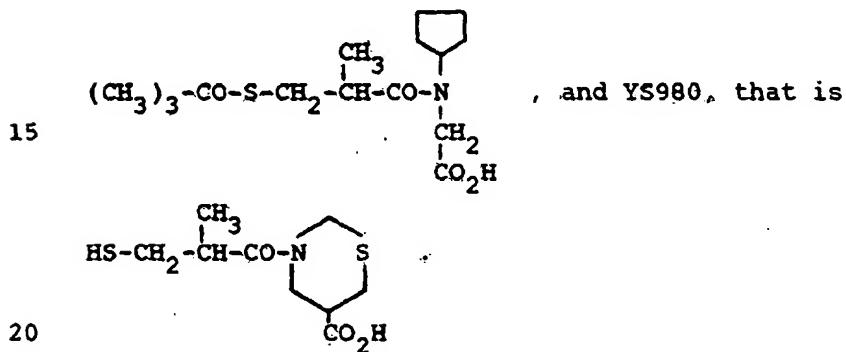
The angiotensin converting enzyme inhibitor 25 which may be employed herein includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in U. S. Patent No. 4,046,889 to Ondetti et al, with captopril, that is,

30 1-[(2S)-3-mercaptop-2-méthylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U. S. Patent No. 4,316,906, with zofenopril



being preferred.

Other examples of ACE inhibitors that may be employed herein include rentiapril (fentiapril, 10 Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983), as well as pivopril, that is



The disclosure of the above-mentioned patents and other references are incorporated herein by reference.

25 Thrombolytic agents which may be employed
 herein include tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen 30 streptokinase activator complex (APSAC, Eminase, Beecham Laboratories).

In carrying out the method of the present invention, the ACE inhibitor alone or in combination with the thrombolytic agent may be administered to mammalian species, such as

monkeys, dogs, cats, rats, humans, etc. during the period of coronary occlusion and/or during the period of reperfusion and/or shortly after termination of the ischemic attack, for example 5 within 1 to 2 hours after the ischemia, within 24 to 48 hours after the ischemia and for weeks and months thereafter.

Although the ACE inhibitor or above combination may be administered systemically, such as orally or parenterally, within 1 hour after the ischemia, it is preferred that the combination be administered locally, as soon after the ischemic attack as possible, to the coronary arteries by catheter such as by arterial angiography or 10 intracoronary injection. 15

With regard to dosage of the ACE inhibitor alone or in combination with a thrombolytic agent, where the drug is administered by arterial angiography, intracoronary injection or intra- 20 venously, ACE inhibitor will be employed in an amount from about 0.005 to about 30 mg/kg/treatment and preferably from about 0.01 to about 3 mg/kg/treatment will be employed. The number of treatments will depend upon the length of the 25 ischemic attack and the progress of reperfusion to achieve normal heart function. Usually, from 1 to 5 treatments per day will be required for as long as contractile dysfunction continues.

The thrombolytic agents will be employed in 30 amounts as indicated in the Physician's Desk Reference (PDR), 42nd Edition, 1988. Thus, Hoechst's Streptase® brand of streptokinase may be administered as follows:

TABLE I
Suggested Dilutions and Infusion Rates

Streptase® (streptokinase) Dosage/Infusion Rate	Streptase® (streptokinase) Vial Content Needed	Total Volume of Solution (mL)	Infusion Pump Rate
I. Intracoronary Artery Administration			
A. Bolus Injection 20,000 IU	1 vial, 250,000 IU*	125	Inject 10 mL
B. Maintenance Dose 2,000 IU/min *sufficient for Bolus Injection and Maintenance Dose			60 mL per hour
II. Intravenous Administration			
A. Loading Dose 250,000 IU/30 min	a) 1 vial, 250,000 IU or b) 1 vial, 750,000 IU	45	90 mL per hour for 30 min
		45	30 mL per hour for 30 min
B. Maintenance Dose 100,000 IU/hr	1 vial, 750,000 IU	45**	6 mL per hour

**If necessary, total volume may be increased, in increments of 45 mL, to a maximum of 500 mL with the infusion pump rate increased accordingly. The total volume of 45 mL or multiple thereof is recommended.

tPA employed herein may be Genentech's ACTIVASE® Alteplase which, as described in the Physician's Desk Reference (PDR), 42 Ed., 1988, Supplement A, pp. A71 and A72 is as follows:

5 ACTIVASE® Alteplase, a sterile, white to off-white, lyophilized powder, is intended for intravenous administration after reconstitution with sterile water for injection, USP. The quantitative composition of the lyophilized

10 product is:

50 mg	20 mg
<u>(29 million IU) Vial</u>	<u>(11.6 million IU) Vial</u>
Alteplase 50 mg	Alteplase 20 mg
(29 million IU)	(11.6 million IU)
15 L-Arginine 1.7 g	L-Arginine 0.7 g
Phosphoric Acid 0.5 g	Phosphoric Acid 0.2 g
Polysorbate 80, less than 4 mg	Polysorbate 80, less than 1.6 mg

20 Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment.

Biological potency is determined by an in vitro clot lysis assay and is expressed in International Units as tested against the WHO 25 standard. The specific activity of ACTIVASE®, Alteplase, is 580,000 IU/mg.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over 30 the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less

than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.

Abbott's Abbokinase brand of urokinase may be administered after heparin dosing of 2,500 to 5 10,000 units IV, in an amount by infusion into the occluded artery at a rate of 4 ml per minute (6,000 IU per minute) for periods of up to 2 hours.

Prourokinase may be administered in conventional dosages normally used in clinical 10 practice such as a 7.5 mg bolus followed by 40.5 mg IV for 1 hour or 66.5 mg IV for 1 hour.

APSAC (Eminase) may be administered in conventional dosages normally used in clinical practice such as a single 30 unit IV dosage.

15 Where the ACE inhibitor or combination is to be administered by angiography, intravenously, or intracoronary injection, it will be formulated in conventional vehicles, such as distilled water, saline, Ringer's solution, or
20 other conventional carriers.

The ACE inhibitor or combination may also be incorporated in a conventional dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary 25 carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory 30 as well.

With regard to such systemic formulations, single or divided doses of from about 5 to about 2500 mg, preferably from about 10 to 2000 mg/one to four times daily, may be administered in systemic

dosage forms as described above for a period sufficient to restore normal heart function.

The dose administered must be carefully adjusted according to age, weight and condition of 5 the patient, as well as the route of administration, dosage form and regimen and the desired result.

Thus, for oral administration, a satisfactory result may be obtained employing the 10 ACE inhibitor in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 25 mg/kg alone or in combination with the thrombolytic agent in an amount within the range of from about 0.01 15 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 25 mg/kg with the ACE inhibitor and thrombolytic agent being employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

20 A preferred oral dosage form, such as tablets or capsules, will contain the ACE inhibitor in an amount of from about 0.1 to about 500 mg, preferably from about 125 to about 200 mg, and more preferably from about 25 to about 150 mg, alone or 25 with the thrombolytic agent in an amount of from about 1 to about 350 mg, preferably from about 2 to about 200 mg, and more preferably from about 30 to about 150 mg.

For parenteral administration, the ACE 30 inhibitor will be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.01 mg/kg to about 1 mg/kg, alone or with the thrombolytic agent

in an amount within the range of from about 0.005 mg/kg to about 20 mg/kg and preferably from about 0.01 mg/kg to about 2 mg/kg.

The composition described above may be

5 administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

10 Tablets of various sizes can be prepared, e.g., of about 50 to 700 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

15 Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

20 25 Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

The following Examples represent preferred embodiments of the present invention.

Example 1

5 An injectable solution for use in administering ACE inhibitor by intracoronary injection by arterial angiography or intravenously is produced as follows:

10 Captopril 500 mg
Methyl paraben 5 mg
Propyl paraben 1 mg
Sodium chloride 25 g
Water for injection qs. 5 l.

15 The captopril, preservatives and sodium chloride are dissolved in 3 liters of water for injection and then the volume is brought up to 5 liters. The solution is filtered through a
20 sterile filter and aseptically filled into
presterilized vials which are then closed with
presterilized rubber closures. Each vial contains 5 ml of solution in a concentration of 100 mg of active ingredient per ml of solution for injection.

25
30 Example 2
Tablets for use in improving post-ischemic contractile dysfunction are prepared as described in Example 1 except that zofenopril is used in place of captopril.

Example 3

An injectable for use in improving post-ischemic contractile dysfunction is prepared as described in Example 1 except that

5 1-(3-mercaptopro-2-D-methylpropanoyl)-L-proline is employed in place of captopril.

Example 4

A captopril formulation suitable for oral administration in improving post-ischemic contractile function is set out below.

1000 tablets each containing 100 mg of captopril were produced from the following ingredients.

15	Captopril	100 g
	Corn starch	50 g
	Gelatin	7.5 g
	Avicel (microcrystalline cellulose)	25 g
20	Magnesium stearate	2.5 g

The captopril and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The 25 Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet to form 1000 tablets each containing 100 mg of active ingredient which is used for improving post-ischemic contractile function.

30

Example 5

The injectable solution for use in administering an ACE inhibitor, may be employed in

conjunction with conventional dosage forms of tPA for reducing myocardial infarct size and improving post-ischemic contractile dysfunction.

5

Example 6

An injectable for use in improving post-ischemic contractile dysfunction is prepared as described in Example 5 except that the ACE inhibitor zofenopril is employed in place of 10 captorpril.

10

Example 7

An injectable solution for use in
15 administering ACE inhibitor and thrombolytic agent
by intracoronary injection, by arterial angiography
or intravenously containing rentiapril as the ACE
inhibitor and streptokinase (conventional dosage)
as the thrombolytic agent is prepared as described
in Example 5.

20

Example 8

An injectable for use in improving post-ischemic contractile dysfunction is prepared as described in Example 5 except that the ACE inhibitor employed is pivopril and the thrombolytic agent employed is urokinase.

The Claims Defining the Invention are as Follows:

1. A method of treating post-ischemic myocardial dysfunction in a mammalian species, which comprises initiating within six hours following myocardial infarction administration of an effective amount of captopril alone or in combination with a thrombolytic agent to reduce or eliminate reperfusion injury.
- 10 2. The method of claim 1 wherein captopril or the combination of captopril and the thrombolytic agent is administered by arterial angiography, by intracoronary injection, intravenously, or orally.
3. The method as claimed in claim 1 or claim 2, wherein administration is initiated within four hours following myocardial infarction.
4. The method of claim 3, wherein captopril or the combination of captopril and thrombolytic agent is administered during coronary occlusion and reperfusion.
5. The method as defined in any one of claims 1 to 4, wherein the thrombolytic agent is tissue plasminogen activator (tPA), recombinant tissue plasminogen activator, streptokinase, urokinase or prourokinase.
6. The method as defined in claim 5, wherein the thrombolytic agent is tissue plasminogen activator or recombinant tissue plasminogen activator.
7. The method as claimed in claim 1, using a composition substantially as hereinbefore described with reference to examples 1, 4 or 5.

DATED: 26 August 1992

E.R. SQUIBB & SONS, INC.
By their Patent Attorneys
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By:

David P Fitzpatrick



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